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(6) That a bacillus identical with *B. influenzae*, both in morphological and cultural characteristics, but capable of differentiation by a study of its pathogenic effects upon animals, is the cause of a septicaemic form of cerebro-spinal meningitis.

(7) That an organism identical in all respects, morphological, cultural, and pathogenic, with *B. influenzae* is a cause of suppuration in the middle ear and the sinuses of the nose.

(8) That a consideration of the foregoing propositions renders it certain that we must in future recognize that the organisms hitherto described as *B. influenzae* are not all identical with it, but, like the streptococci, staphylococci, and the colityphoid family, belong to a group the various members of which possess very different pathogenic powers.

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HEREDITARY HAEMOPHILIA :

DEFICIENCY IN THE COAGULABILITY OF THE BLOOD THE ONLY IMMEDIATE CAUSE OF THE CONDITION¹

By THOMAS ADDIS

IN 1896 Wright first definitely established the fact of the delayed coagulation of the blood in this disease. Since then it has been confirmed by Sahli, Morawitz and Lossen, Weil, Baum, Kottmann and Lidsky, Nolf and Herry, and others. No one using modern methods has found a normal coagulation time in haemophilic patients. But the constancy of this pathological feature does not exclude the possibility that there are other causes at work in producing the symptoms of the disease. There are certain difficulties in the way of accepting it as the sole cause. Indeed, when some of the clinical phenomena are considered, it would seem that a deficient coagulability of the blood is inadequate in itself to explain all the facts. If the blood in haemophilia were incoagulable then indeed it would not be necessary to look further. But it is not. On the contrary, very large clots form in the wounds of these patients, though blood may continue to ooze from them for hours or days. If then the diminution in coagulability is not of such a degree as to prevent coagulation in the wound, how can it be regarded as the direct cause of the continuance of the haemorrhage? Again, how does it account for the fact that the wound cavity may soon be filled with clot which completely arrests the bleeding, and that nevertheless hours later haemorrhage may recur and continue indefinitely? Surely during the period when the bleeding had ceased, the blood in the wound must have had ample opportunity for complete coagulation? These difficulties might be explained by assuming that there was a deficient formation of fibrin, so that the clot was loose and easily dislodged; but this appears to be negatived by the results of Sahli's experiments. He showed that, *ex vitro at least*, the fibrin formed in the delayed coagulation of haemophilic blood was as great in amount as that produced in the more rapid clotting of normal blood, and that it is impossible to distinguish one clot from the other, both are equally firm and dense.

Wright, though holding fast to the deficient coagulability as the proximate cause, recognizes that it does not explain all the facts. Sahli, who attempts a complete theory of the condition, is obliged to assume a hypothetical chemical defect in the tissues of the vessel walls, which consists of an absence in them of the substance, thrombokinas, which normally initiates the process of coagu-

¹ The work in connexion with this paper has been done under the conditions of tenure of a Carnegie Research Scholarship.

lation. In this way he explains the continuance of haemorrhage in spite of clotting in the wound, for no clot forms in the ruptured vessels themselves, although it may occur when the blood leaves them and comes into contact with the extravascular tissues of the wound. This assumption, however, is purely speculative and unsupported by any experimental data. Morawitz and Lossen found that the addition of thrombokinase to haemophilic blood causes a very rapid coagulation. From this fact they conclude that the delay in coagulation is due to a deficiency of thrombokinase in the tissues in general. In a subsequent paper I shall bring forward results from which it may be concluded that they are mistaken in this view, but assuming it to be correct, the above objections still remain to the defective coagulation thus explained being the sole cause of the phenomena seen in the haemorrhages in haemophilic subjects. Sahli's theory is certainly the most complete, and yet Dahlgren in a paper published last year, in which he describes the death from loss of blood of three haemophiles, is unable to accept it. He asks how, if it is true, the recurrence of bleeding after its complete cessation is to be explained, and why the amount of bleeding should be so variable, sometimes continuing for a long time from a slight cut, at other times ceasing more quickly from a much more extensive wound. The general opinion of most of those who have had an opportunity of watching the onset and development of haemorrhages in haemophilia is that there must be some other factor at work, such for instance as an abnormal fragility of the capillaries, whose mode of action must be made clear before a complete explanation of all the phenomena of the disease can be said to have been attained.

All are agreed, however, that the defect in coagulation is the only constant pathological sign of the disease. The object of the present paper is to bring forward evidence that it is not necessary to go beyond this fact in the search for the proximate cause of haemophilia. It will be shown that there is a direct relation between the severity of the symptoms and the degree of retardation of coagulation; that after the lapse of some time the blood flowing from a wound in a haemophilic still shows the characteristic delay in clotting, and that this is well marked even in recurrent haemorrhage from wounds in which coagulation has taken place. Finally, the peculiarity of the clot which forms in haemophilic wounds is described, and it is shown how bleeding may continue in spite of it, or may cease only to recur. This abnormality in the nature of the coagulation arises as the direct result of the great prolongation of the time required for coagulation to complete itself. This therefore, it is maintained, is the sole proximate cause of haemophilia, sufficient in itself to explain all the symptoms.

I. The coagulation time of the blood.

Twelve cases were examined. They were descended from six different haemophilic stocks in Scotland, England, and Germany. In none of these families was there any known instance of a departure from the characteristic

type of transmission, i.e. through the females to the males. Full clinical accounts of several of these cases have been or will be published. A short sketch of their histories will be found at the end of this paper.

The coagulation time of the blood of people in health is constant. The actual time required depends on the temperature and the method by which it is estimated. The method mainly used was a modification of McGowan's method (1), and the temperature was 20° C. Under these circumstances normal blood coagulates in 10 minutes. Variations between 9 and 11 minutes occur and are due to experimental error. These figures are based on observations (1) in which every coagulation time represented an average of three consecutive estimations, but in the following times found in haemophilic patients each figure is a single observation and not an average.

Case I.

Date.	Coagulation time in minutes and seconds.	Date.	Coagulation time in minutes and seconds.	Date.	Coagulation time in minutes and seconds.
Sept. 18	9. 0	Sept. 23	17.45	Sept. 25	15.15
	12.30		19.15		13.45
	10.45		12.45		13.45
Sept. 20	16.15	Sept. 24	9.30	Sept. 27	15.45
	16.45		9.45		16.30
	21.45		11.30	Oct. 11	17.30
Sept. 21	12.15	(5 hours later)			18.30
	11.15		15.45		16.30
	15.15		14.15	Oct. 18	18.30
Sept. 22	13. 0		15.45		21. 0
	15. 0				20. 0
	15. 0				

Case II. Three estimations were made. Times of 16 min. 15 sec., 13 min. 45 sec., and 15 min. 45 sec. were obtained.

Case III.

Date.	Coagulation time in minutes.	Date.	Coagulation time in minutes.	Date.	Coagulation time in minutes.
Aug. 21	62	Aug. 25	80	Sept. 8	55
	59		52	Sept. 10	55
Aug. 22	53	Aug. 26	74		55
	58		61	Sept. 11	57
	50	Aug. 30	86		84
	50		87	Sept. 18	54
Aug. 23	50	Aug. 31	91	Sept. 19	71
	51	Sept. 4	71		60
	49		62	Sept. 23	77
Aug. 24	63	Sept. 5	75		75
	70		87		

Case IV.

Date.	Coagulation time in minutes.	Date.	Coagulation time in minutes.	Date.	Coagulation time in minutes.
Sept. 19	58	Sept. 22	90	Sept. 23	44
	59		78		96
	63		84		
			96		

Case V.

Date.	Coagulation time in minutes.	Date.	Coagulation time in minutes.	Date.	Coagulation time in minutes.
Sept. 15	40	Sept. 16	56	Sept. 20	79
	36	Sept. 18	59		80
	38		49	Sept. 23	43
					60

Case VI. The coagulation times were 72 min. and 73 min. Five days later a time of 87 min. was found.

Case VII. In this case two estimations gave times of 71 min. and 55 min.

Case VIII. The times were 70 min., 74 min., and 72 min.

Case IX. The times were 79 min., 92 min., 85 min., and 83 min.

Case X. The times were 71 min., 63 min., 61 min., 75 min., 68 min., and 64 min.

Case XI. The coagulation time with my method was as a rule between 30 and 40 minutes.

In this case the method of Morawitz and Bierich was also used. A hollow needle sterilized by heating in liquid paraffin was inserted into the median basilic vein, and about 2.5 c.c. of blood was run into each of a series of test-tubes, which were then kept at a constant temperature until they could be inverted without spilling. The coagulation time was the period elapsing between this point and the time at which the blood was drawn. When the temperature was 30° C. times of 43 min., 45 min., 47 min., 48 min., 47 min., 47 min., 44 min., 46 min., 44 min., 42 min., and 42 min. were obtained. An experiment carried out under the same conditions on normal blood gave times of 18 min., 20 min., 20 min., 18 min., 17 min., 17 min., 17 min., and 17 min.

A week later the coagulation time was again taken with this method, but the temperature was 37° C. The results were 46 min., 52 min., 52 min., 45 min., 51 min., and 53 min. With normal blood the times were 13 min., 12 min. 45 sec., 14 min. 30 sec., 12 min. 15 sec., 14 min., and 13 min. 45 sec.

Case XII.

Feb. 24. 70 min., 65 min., 75 min., 80 min., and 72 min.

Feb. 28. 86 min., 60 min., 45 min., 87 min., 86 min., and 65 min.

March 2. 75 min., 80 min., 85 min., 63 min., and 89 min.

March 4. 53 min., 59 min., 58 min., 70 min., 75 min., and 57 min.

These results show conclusively, therefore, that there is a delay in the coagulation of haemophilic blood, a delay which in some cases is very pronounced and which far exceeds any retardation of coagulation observed in other diseases (2).

But although the fact that there is a great delay in coagulation is quite clearly and definitely shown, the actual figures are obviously only very approximately correct, for there are often wide variations even in the results of consecutive observations. The experimental error must certainly be a very large one. Nevertheless there can be no doubt as to the substantial reliability of the method, when a number of determinations are made and the average is taken as representing the coagulation time. In Case XII the coagulation times were taken by this method, and also with the method of Morawitz

and Bierich, at a time when wide variations in coagulability were taking place as the result of therapeutic injections, and the results agreed well with each other. Smaller variations, such as perhaps occur under physiological conditions in these patients, are, however, obscured by the experimental error. The clinical histories of some cases of haemophilia suggest a certain periodicity in the appearance of the symptoms, and it is quite possible that these depend on variations in the coagulability of the blood. To determine whether there are in reality changes in the time, Dr. Finlay and I have commenced independent observations on the same days with the two methods in Case XII. So far our results agree closely and show some degree of variation, but the point cannot be said as yet to be settled.

II. *The relation between the severity of the symptoms and the coagulation time of the blood.*

Clinically the cases fall naturally into three groups. The first is that in which the patients were scarcely ever free, for any length of time, from some sign or other of the disease, even in the absence of any traumatic accident greater than those inseparable from ordinary life. Cases III, IV, V, VI, VII, VIII, IX, X, and XII are included in this group. None of them, during the period when they were under observation, was suffering from any severe or disabling haemorrhage, but in all of them very slight degrees of trauma were sufficient to induce bleeding. For example, Case III knocked his hand against an iron rail, and although the force with which he did so was not sufficient to lead to any appreciable pain, effusion took place into the metacarpophalangeal joint. He twisted his knee slightly coming downstairs, and it became swollen with blood. On another occasion an effusion into the knee occurred, although he could not remember having hurt it at all. In Case IV also the slightest injury to his knees gave rise to pain and swelling, and the signs of fluid in the joint. In him and in Case V small puncture wounds in the fingers were followed by the development of haematomas. Case VI brushed his arm against the door when leaving a room, and next day a bruise had appeared. Case XII was confined to bed, but even here there was bruising which was evidently the result of his raising himself from the bed on his elbows. In all these cases it was the exception not to find a bruise on some part or other of the body, or an effusion into one or more joints.

The second group is that in which trivial accidents did not lead to observable haemorrhage. Case XI is the only one who comes in this group. He was often free from all symptoms for weeks on end. The maximum of trauma which led to bruising in him was considerably greater than that necessary to produce it in the cases of the first group. For instance in Case VI the application of a moderately tight bandage on the arm was followed by bruising, yet in Case XI, though bandages quite as firm were often applied, there was never the least trace of bruising. Again, on one occasion in drawing off blood from a vein

in the arm in Case VI, the needle, instead of going directly through the skin into the vein, ran into the subcutaneous tissues. A small haematoma appeared and there was deep staining of the skin from the wrist to the axilla. A similar accident occurred once or twice with Case XI, but there was never any haematoma and the amount of bruising was very slight.

In the third group a still greater degree of injury was required to lead to any appreciable amount of haemorrhage. The only practical difference between the patients in this group and ordinary individuals was that on the occurrence of such a wound or injury as would always produce an appreciable amount of bleeding in any one, the bleeding in them persisted for a longer time. Cases I and II are in this group. In both of them there had been no sign for years that they were in any way different from other people. This, however, was only due to the fact that for a long time they had not sustained any severe injury. For when Case I had a tooth extracted the bleeding persisted for 10 days, and showed that his long freedom from symptoms was only a matter of degree, and was not an indication that he was completely normal.

As regards the severity of the disease, therefore, the cases are clearly separable into the three groups of severe, moderate, and slight cases. If the deficiency in coagulability is in itself sufficient to explain the symptoms, it would follow that the severer the manifestations of the disease the longer the coagulation time would be, and vice versa. That such in fact is the case will be seen in the following table, in which each case is grouped according to the degree of incidence of the clinical symptoms, and the average coagulation time of all the observations taken on the case is given :—

Severe symptoms.	Moderate symptoms.	Slight symptoms.
Case III = 68 min.	Case XI = 36 min.	Case I = 15 min.
„ IV = 74 „		„ II = 15 min. 15 sec.
„ V = 54 „		
„ VI = 77 „		
„ VII = 63 „		
„ VIII = 72 „		
„ IX = 85 „		
„ X = 67 „		
„ XII = 70 „		

III. *A consideration of the process of coagulation in normal and haemophilic wounds.*

The coagulation times which have been given are a measure of the time required for the clotting of the first drop of blood issuing from a small puncture wound, but they do not give any indication of the changes in coagulability which take place in blood flowing from a wound, from the moment when it is inflicted up to the time when such an amount of clot has formed that the bleeding ceases. Under normal circumstances there is a rapid and progressive increase in the coagulability of each successive specimen of blood; the first drop takes the longest time and the last coagulates practically instantaneously. But

before comparing this with the results obtained by similar observations on blood from haemophilic wounds, it will be of advantage briefly to consider the present position as regards the physiology of coagulation and the explanation which is advanced of this progressive acceleration of the rate of coagulation.

There have been in the past many theories of the coagulation of mammalian blood which are now discredited or greatly modified, but certain facts remain, though the interpretation of their meaning and significance has changed. These essential facts can be put very shortly. Coagulation is the formation of fibrin. There are four factors necessary—fibrinogen, prothrombin, thrombokinase, and calcium. By the interaction of the last three thrombin is produced, and thrombin acting on fibrinogen precipitates fibrin. Fibrinogen is a globulin in solution in the plasma. The action of thrombin upon it is generally believed to consist in a cleavage of the molecule into two parts—serum-globulin, which is soluble, and fibrin, which is insoluble. Prothrombin² is a substance of unknown chemical constitution, present in circulating blood. In itself it has no action on fibrinogen, but in the presence of thrombokinase and calcium, after a certain interval of time, a change is found to have taken place in its physical and chemical properties and the new body, thrombin, is formed, whose action on fibrinogen has been noted. Thrombokinase³ is also of unknown chemical constitution. It is not found in the plasma of the circulating blood, but is present in the tissues, particularly those rich in nucleo-proteins, and in the formed elements of the blood. Without it no thrombin can be formed. The greater the quantity of thrombokinase added to the blood from the tissues or formed elements, the more rapid is the change of prothrombin into thrombin. Calcium salts are also essential for the formation of thrombin. Thrombin, the result of the action of thrombokinase and calcium on prothrombin, is often called fibrin ferment, but this is an unfortunate term, since it does not possess all the properties of a ferment. Thus it acts quantitatively, that is to say, a measured quantity will coagulate a certain definite amount of fibrinogen and no more. In the act of coagulating the fibrinogen it becomes attached to the fibrin, and most of it is precipitated with it. That part which remains free after all the fibrinogen has been coagulated disappears after a short time. This is generally ascribed to the action of a substance in the plasma which is termed anti-thrombin. Although thrombokinase and calcium are necessary for the building up of thrombin, they are not required for its action once it has been formed. All fibrinogen-containing fluids, whether they contain thrombokinase and calcium or not, are coagulated when thrombin is added to them. Time is required for the formation of thrombin, but the action of thrombin once formed is practically instantaneous.

Work on coagulation has centred round the theory which Schmidt advanced towards the end of last century, after a lifetime of work devoted to this subject.

² Prothrombin was the term originally used by Alexander Schmidt, but it has been called thrombogen by Morawitz and plasmozym by Fuld.

³ Corresponds to the zymoplastic substance of Schmidt, the cytoplasm of Fuld, the tissue-coagulin of Loeb, and the thrombozym of Nolf.

Although further research has shown him to be mistaken in many details, yet the general outline of his theory remains and is now only more firmly established. Morawitz and Fuld, as the result of much painstaking work, were able to clear away many errors and misconceptions, but their elaboration of Schmidt's theory is recognized by them as not being entirely final. There remained unexplained and puzzling discrepancies in the work of different investigators, and some details in the various phenomena of coagulation were still not quite clear.

There is now, however, a theory of coagulation founded on experimental work of the most conclusive character which explains all these difficulties. Mellanby's work ends a period in the history of the gradual growth of knowledge in this department; it completely answers the old questions, and in doing so raises new problems for the future. The reason for his success lay in the fact that he was able to isolate the different factors concerned in coagulation, while the obscurity and variability of the older results were due to a want of precise knowledge as to the contents of the fluids with which these results were obtained. Solutions which were considered to contain only one of the constituents necessary for coagulation were often mixtures of two or more of these principles in varying proportions. It is indeed to be wondered at that with such confusion at the very basis of their work, they should, nevertheless, have arrived at conclusions which lie so near the truth. As an example of this confusion, Schmidt's thrombin, which has been accepted as the standard thrombin solution, is now proved to contain a varying quantity of thrombin, sometimes none at all, and its coagulative action is shown to be often due to the thrombokinase and calcium, whose presence in it were unsuspected. The meta-thrombin, on which Morawitz in his theory lays such stress, is proved to be thrombokinase. But the most important fact that Mellanby has established, and the one which more than any other makes clear the difficulties into which other observers have been led, is the relation which exists between fibrinogen and prothrombin. Fibrinogen solutions were usually assumed to contain fibrinogen only, whereas in reality prothrombin was present. In whatever way fibrinogen is obtained, prothrombin is always found associated with it,⁴ and further, the amount of prothrombin is directly proportional to the amount of fibrinogen. The prothrombin is in a condition of absorption in the fibrinogen molecule, and the only way in which a solution of prothrombin can be obtained free from fibrinogen is by coagulating fibrinogen by the addition of a foreign thrombin. The molecule is then broken up, fibrin is precipitated, prothrombin is set free, and is found in the fluid expressed from the clot. Such a fluid has no coagulating action, except in the presence of calcium salts and thrombokinase, when it becomes a thrombin solution with very marked coagulating powers.

Mellanby's theory, very shortly expressed, is as follows: The circulating

⁴ Prothrombin appears to be more easily destroyed than fibrinogen, and so it comes that it is possible to prepare fibrinogen solutions in which the contained prothrombin is no longer capable of activation to thrombin. Such solutions coagulate only when preformed thrombin is added to them.

blood contains fibrinogen with its absorbed prothrombin, calcium salts, and anti-thrombin. No coagulation takes place because of the absence of thrombokinase. When the tissues are wounded, the injury or destruction of the cells leads to the setting free of thrombokinase. In its presence the calcium salts unite with the prothrombin, and thrombin is formed. On account of the close molecular relation which exists between this newly formed thrombin and the fibrinogen it escapes the neutralizing action of the anti-thrombin, and fibrin is quickly formed by its action on the fibrinogen. Most of the thrombin is precipitated with the fibrin. Any fresh blood forcing its way through the clot is coagulated by thrombin, and prothrombin is thus set free, but if no thrombokinase reaches it no fresh thrombin is formed. The production of thrombin is therefore strictly limited to the sphere of the thrombokinase. That part of the thrombin which is not carried down in the fibrin is gradually neutralized by the anti-thrombin. 'The whole mechanism of coagulation is admirably adapted to produce large and rapid clotting within a wounded area, but to stop the process immediately beyond the confines of the injured tissues.'

Mellanby's theory is in the main that of Morawitz and Fuld, simplified, and at some points enlarged, and now for the first time freed from uncertainty and speculation. In the light of this theory the process of coagulation in wounds in normal and in haemophilic people may now be compared.

The following figures represent the changes in the coagulation of blood flowing from a wound in a normal person. A deep puncture was made into the thumb and the coagulation time of successive specimens of the outflowing blood was determined.

Length of time after making the wound at which the specimen of blood was taken.		Coagulation time.		Remarks.
min.	sec.	min.	sec.	
0	0	12	45	
0	30	9	30	
1	15	3	15	
2	15	1	30	
2	30	0	15 ?	
2	45	—	—	No more blood could be obtained

How is the rapid increase in the coagulability of each successive specimen of blood to be explained? Of the four factors in coagulation—fibrinogen, prothrombin, calcium, and thrombokinase—the first three, being already present in the blood, were necessarily constant. The only variable was the thrombokinase added to the blood from the injured tissues. The first specimen of blood spurting out instantaneously from the capillaries was in contact with the tissues for only a very short time, and, as a consequence, took up a small amount of thrombokinase. With each successive specimen not only was the flow of blood becoming progressively slower but more and more thrombokinase had time to exude from the injured tissue cells. Now the rate of the change of prothrombin into thrombin, other things being equal, depends on the quantity of thrombokinase; the more thrombokinase the more rapid the production of thrombin.

The increasing coagulability, then, was due to increasing amounts of thrombokinase. But this does not account for the instantaneous coagulation of the last specimen.⁵ For even with large quantities of thrombokinase the formation of thrombin requires some time, it is not instantaneous. Only where preformed thrombin is added to it does blood coagulate immediately. But such preformed thrombin must have been derived from the previous coagulation of blood in the wound. Further the clotting must have been only partial, or no more blood would have flowed. This free thrombin came from the coagulation of the blood adherent to the sides of the wound. There the flow was slowest and there the concentration of thrombokinase was highest. It thus came about that the prothrombin of this part of the blood had time to change into thrombin before it was forced out of the wound. Immediately this was accomplished the newly formed thrombin coagulated the fibrinogen with which it was associated. Most of it was precipitated with the fibrin, but enough escaped partially to clot the blood in the centre of the wound, which slowly escaped from the wound, and was the last specimen obtained. But this was the end of the haemorrhage. The activation of prothrombin was proceeding, and immediately afterwards enough thrombin had been set free to completely coagulate all the blood in the wound. No more blood could then be forced out even by pressure.

The cessation of bleeding, then, was due to two forms of coagulation, which for convenience of description may be called primary and secondary. In the primary coagulation the blood was coagulated by the activation of its own inherent prothrombin. Each molecule of fibrinogen was acted on by thrombin formed from the prothrombin which was present within the molecule itself. In the secondary coagulation the blood was coagulated by preformed extraneous thrombin derived from the primary coagulation of another part of the blood. Its own prothrombin took no part in the process.

That is the course of events as they occur in a wound in a normal person. What happens when a similar wound is made in a haemophilic? A puncture wound, as far as possible of the same depth and extent, was made into the thumb of Case III and the coagulability of successive specimens of blood was estimated in the same way.

Length of time after making the wound at which the specimen of blood was taken.		Coagulation time.		Remarks.
min.	sec.	min.	sec.	
0	0	80	0	
0	15	60	0	
0	30	44	0	
0	45	32	0	Bleeding stopped ⁶
2	45	28	0	Expressed blood
7	0	12	30	Expressed blood
12	0	—	—	No more blood could be expressed

⁵ The coagulation time is put down as 15 sec., but this is simply the shortest time in which it was possible to determine the presence of fibrin.

⁶ This cessation of haemorrhage was due to mechanical causes. Whenever the pressure of the outflowing blood fell sufficiently, the skin closed over the wound and prevented the exit

Here also there is the same progressive increase in coagulability. It happened that the very last drop of blood before complete coagulation set in was not obtained, but, if it had been, the instantaneous coagulation seen in the last drop from the wound in the normal person would also have been observed here. The difference is one of degree only, though it is a very marked one. For the last specimen of blood obtained, some of which had remained in the wound in contact with the tissues for nearly five minutes, did not show the immediate coagulation which was found in normal blood after two and a half minutes in spite of the fact that in that wound the blood was being constantly forced out by fresh blood. The difference is much greater than the figures themselves indicate, and reveals a great delay even under these most favourable circumstances in the formation of thrombin in haemophilic blood. It may be objected that this is not the only explanation, for thrombin might have been formed, but yet have been inefficient or unable to act because of some fault in haemophilic fibrinogen. I hope to enter fully in a subsequent paper into the cause of the delay of coagulation in haemophilic blood, and there I shall show in detail that haemophilic blood is quite as easily and readily coagulated by haemophilic thrombin as is normal blood by normal thrombin. The only possible explanation then is that the thrombin took an abnormally long time to form.

This fact alone goes some way towards explaining the length of time during which haemorrhage may continue in haemophilia, although, as will be shown, it is not in itself a sufficient reason. In this particular instance, bleeding was stopped mechanically by the closing of the skin over the mouth of the wound, and time was given for thrombin to form in the blood enclosed in the cavity of the wound. If, however, an incision had been made of such an extent as to allow the skin to retract and leave the wound open, it is easy to see that bleeding might have continued for a long time without there being any chance of the blood coagulating.

But the special characteristic of haemorrhages in haemophilia, and the point which is difficult to understand, is that in spite of the sometimes massive formation of firm clots in and around the wound, the bleeding still continues or ceases for a time only to recur. Thus in Case I, who had had a tooth extracted, the bleeding went on for ten days, and, but for treatment, would have continued for a still longer time, although large clots formed and adhered firmly to the contused gum. Fresh blood filtered up slowly and continuously through the clot and ran over into the mouth. How is the continuance of bleeding to be explained in such a case? How can it be attributed to any deficiency in the coagulability of the blood since firm coagulation has nevertheless obviously taken place?

And yet, paradoxical as it may appear, it is because of the coagulation that the bleeding continues. In such wounds in haemophiliacs coagulation is local instead of general. Only that part of the blood which is in immediate contact

of any more blood. On account of this plugging of the wound by the elastic recoil of the tissues it is possible with safety to introduce small hollow needles into the veins of haemophiliacs for the purpose of obtaining blood.

with the tissues coagulates. In doing so it forms a firm barrier against the access of more thrombokinase to the blood in the central part of the wound. Bleeding continues through a funnel of fibrin lining the sides of the wound. The reason why such a partial coagulation occurs in haemophilia will be made clearer by giving the details of an experiment on the effect on the coagulation time of haemophilic and normal blood of adding varying amounts of thrombokinase.⁷ This was done by running various dilutions of thrombokinase through the glass tubes immediately before they were filled with freshly drawn blood. That amount of thrombokinase which remained adhering to the walls of the tube mixed with the blood and exerted its effect. The temperature was 20° C.

Thrombokinase solution.	Coagulation time of the blood of Case III. (The coagulation time without the addition of any thrombokinase was 68 minutes.)		Coagulation time of the blood of Case IV. (The coagulation time without the addition of any thrombokinase was 74 minutes.)		Coagulation time of the blood of a normal person. (The coagulation time without the addition of any thrombokinase was 10 minutes.)	
	min.	sec.	min.	sec.	min.	sec.
0.4 %	4	30	2	30	2	30
	3	0	2	30	2	0
0.1 %	5	30	5	15	3	30
	6	30	4	15	3	0
0.5 %	7	30	7	0	4	15
	8	0	7	0	4	0
0.25 %	13	30	9	0	5	45
	10	30	8	15	5	15
0.125 %	24	45	17	0	6	30
	22	30	—	—	5	15
0.062 %	36	0	33	0	6	15
	41	0	23	0	5	45
0.031 %	47	0	48	0	8	45
	45	0	75	0 (?)	8	0

From these figures it is seen that while with large amounts of thrombokinase coagulation may be as rapid as that of normal blood, with smaller amounts, even such as are sufficient notably to accelerate the coagulation of normal blood, there is still a very prolonged coagulation time.

This has an evident bearing on the question of the continuation of haemorrhage in haemophilia in spite of the presence of clots in and around the wound. When an incision is made through the skin the blood streams from the vessels and fills the cavity caused by the retraction of the tissues. Thrombokinase comes from the injured cells and mixes with the blood which is in contact with the sides of the wound. It is here that there is the greatest concentration of thrombokinase and here also that the flow of blood is somewhat retarded. The coagulation of the part of the blood in contact with the tissues is thus markedly accelerated, so that it may coagulate and leave a film of fibrin adherent to the tissues. But in the more centrally situated blood the concentration of

⁷ The thrombokinase was obtained from a human testicle. The gland was stripped of its coverings and weighed immediately after its removal from the body. It was then ground up in a mortar with sand, extracted for some hours with that amount of distilled water which gave a solution of 4 per cent, and finally filtered and heated to 100° C.

thrombokinase is not so great. Now it has been shown in the above experiment that the formation of thrombin in haemophilic blood takes a long time even in the presence of considerable amounts of thrombokinase. This part of the blood is therefore driven out of the wound before sufficient thrombin has formed to coagulate it. The pressure of the out-flowing blood is sufficient to wash away the thrombokinase from the mouths of the severed vessels and continually to drive out before it the blood in the central part of the wound, which, though it does not contain so much thrombokinase, only requires time to coagulate. The layer of fibrin on the sides of the wound increases in thickness until the point is reached at which the amount of thrombokinase which penetrates through it is no longer sufficient to induce rapid coagulation. But this is not a complete picture of what occurs, for no account is taken of the thrombin liberated in the coagulation of this peripheral blood. There is no excess of anti-thrombin in haemophilic blood,⁸ and the question, therefore, arises why, once some thrombin has been formed, coagulation does not occur throughout all the blood in the wound. This is simply a question of degree. Rettger has shown very clearly how the coagulation of blood by thrombin is a purely quantitative process, and I have repeatedly confirmed this point. A certain minimum amount of thrombin is necessary to produce any visible coagulum at all. As the amount is increased the quantity of fibrin formed grows greater. Thrombin, therefore, does not act in this respect in the manner of a ferment, and though thrombin is produced in the wound the question whether or not it will coagulate the blood in the central part of the wound depends entirely on the quantity. If the coagulation at the periphery of the blood stream is taking place very slowly only small quantities of thrombin will be produced at any given moment, the coagulation induced will be partial, and the soft loose clot will be driven out with the stream of blood. Or, although partial, the clot may remain in the wound and stay to some extent the main force of the outflow, while still allowing some blood to trickle through its meshes. This is the usual condition in a wound of moderate severity in haemophilia. There are thus two clots in the wound: the one peripheral and due to primary coagulation by the activation of the prothrombin by means of thrombokinase; a second central and distinct from the other, not only in its position, but in the fact that it is a secondary coagulation due to extraneous thrombin liberated from the peripheral clot. Such a secondary clot has no power to induce coagulation. It contains no thrombokinase, and when all the thrombin has been neutralized, blood coming straight from the vessels and free from thrombokinase may ooze through it without being in any way affected.

I do not maintain that in every case of prolonged bleeding in haemophilia there is this absolute distinction between the primary and secondary clots. Probably a certain amount of thrombokinase will be present even in the blood in the centre of the wound, for it must be remembered that thrombokinase arises not only from the tissue cells, but that a certain amount is also derived from the

⁸ The grounds for this statement will be given in a subsequent paper.

formed elements of the blood when they are injured. But even though the sealing-off of thrombokinase is not absolute, the blood may take a very long time to coagulate, even if the flow of fresh blood from the vessels has been stopped by the secondary coagulum. With minimal amounts of thrombokinase the coagulation of haemophilic blood may take many hours to complete itself. If, during this period, the secondary coagulum is dislodged from the mouths of the vessels, by, for instance, a sudden rise of blood pressure, the bleeding will recur, and—since the access of large amounts of thrombokinase from the tissues is prevented by the peripheral primary layer of clot—may continue indefinitely.

This explanation of the reason for the continuance of bleeding in haemophilia in spite of the occurrence of coagulation in the wound was suggested by observations made on a haematoma which developed in Case IV. Some puncture wounds rather deeper than usual had been made into the extensor surface of the right thumb, in order to collect some blood from which to obtain serum. Bleeding ceased almost immediately, but three-quarters of an hour later, while he was washing his hands in hot water, quite brisk haemorrhage started from one of these wounds. It was apparent then that the stopping of the bleeding soon after the wound had been made had not been due to coagulation. It must rather be attributed to the elasticity of the skin, which by its recoil led to the close apposition of the lips of the wound and so to a mechanical prevention of further loss of blood. For when the skin was relaxed by hot water the wound opened and bleeding began again. Some cotton-wool steeped in freshly shed normal blood was applied and pressure exerted by a bandage. No blood soaked through, but when, three hours later, it was taken off, bleeding began again. Two estimations of the coagulability of the blood streaming from the puncture gave times of 48 min. and 49 min. Pressure again stopped the bleeding until an hour and a half later, when he took a hot bath. Shortly afterwards he came to me because blood was coming through the bandage. Blood was flowing freely, and whenever the lips of the wound were separated, a jet of blood spurted out, indicating that a small arteriole had been cut. The coagulation times of three specimens of blood from the wound were 43 min., 61 min., and 51 min.

Now it was inconceivable that after all these hours there had not been ample time for the blood remaining in the wound to completely coagulate if it was in contact with the tissues and thus taking up large quantities of thrombokinase from them. In Case III, as has been shown, complete coagulation in the wound took place in twelve minutes. The only explanation appeared to be that in this case complete coagulation had only occurred locally. Only the film of blood in direct contact with the tissues, in which therefore the concentration of thrombokinase was high, had clotted. The amount of thrombin set free from this primary coagulation had not been sufficient to completely coagulate the blood in the centre. A small pool of partially coagulated blood was left there in communication with the cut vessel and cut off from the tissues, and therefore from the access of thrombokinase by the peripheral primary clot. When the wound opened, this central blood was washed out and the flow

continued until pressure closed the lips of the wound again. It must be remembered that the coagulation times given of blood flowing from the wound do not represent the actual time which each particular specimen of blood would have taken to coagulate if it had remained in the wound. For the contact of blood with glass, as I have shown elsewhere (3), has a great effect in accelerating coagulation on account of the injurious action it exerts on the formed elements, which leads to the setting free of thrombokinase from them. In the wound itself there was no such foreign body, and if the shutting off of thrombokinase was absolute, and all the thrombin from the primary clot had been neutralized, the blood in the centre of the wound would have remained fluid indefinitely.

The subsequent course of events appeared to confirm the correctness of this view. Pressure maintained for two days prevented any further bleeding, and when the bandage was removed the skin was found to have healed over the wound, but a small haematoma about 2 mm. in diameter had formed. Day by day this increased in size until on the sixteenth day it was a swelling as large as a walnut. Fluctuation was readily elicited in it. By this time the skin had begun to split, and blood was oozing from a rupture in a fibrinous membrane which was thus exposed. An incision was made into the swelling, and after cutting through a tough layer of fibrin the central portion was found to consist of a loose clot, in the meshes of which there was much uncoagulated blood. The haematoma thus showed itself to be in reality a false aneurism, and the gradual increase in size to have been due to a slow stretching of the sac of fibrin by the pressure of blood from the severed arteriole, with which it was in direct communication. The loose central clot was due to partial secondary coagulation. All thrombin must long ago have disappeared from it, not only by attachment to fibrin but also by neutralization by anti-thrombin. It would never have grown any firmer, and it had no coagulating effect on fresh blood flowing through it from the cut vessel. Surrounding it on all sides and entirely cutting it off from contact with the tissues, and thus from all chance of the addition to it of thrombokinase, was the primary clot. It was extremely dense and firm, and was only separated from the tissues with some difficulty. After this had been done, a strong solution of human thrombokinase was applied to the raw area and continuous pressure kept up for some time. There was no further bleeding and rapid healing ensued.

This type of coagulation in a wound is the direct result of the great delay in the formation of thrombin. The primary clot is laid down very slowly and gradually, because it can only occur where the concentration of thrombokinase is very high. It thus comes about that at no time is there a sufficient amount of thrombin liberated from it to produce complete secondary coagulation in the rest of the blood. In a person in whom the coagulation time of the blood is normal, as has been shown, thrombin rapidly forms in the presence of much smaller quantities of thrombokinase than are necessary to produce thrombin from haemophilic blood within a reasonable time. The primary clot is thus

much larger, and an amount of thrombin is immediately set free from it which is more than enough to cause complete coagulation of the remaining blood.

But although it may be granted that the deficiency in the coagulability of the blood is sufficient in itself to explain the phenomena observed in the persistent or recurring haemorrhages from wounds which are seen in haemophilia, are there no other clinical manifestations of the disease which seem to point to the existence of some further factor in the causation of the condition? It may be said, for example, that the very slight degree of trauma which will produce extensive bruises, or large effusions into joints in severe cases, is an occurrence which requires some further explanation than any mere fault in the blood itself. For before haemorrhage can occur there must be a lesion of the vessels. Surely the varying degrees of trauma which suffice to produce bruising in cases in which the condition is present in a severe, moderate, or slight form, point to a varying liability to rupture in the capillaries? It is true that there is no histological evidence of the presence of any constant or characteristic change in the walls of the vascular system in haemophilia, but an undue fragility of the capillaries might well exist, although it was not marked by any change in their microscopical appearance. Fragility of the capillaries is in itself an undoubted cause of haemorrhage. It is not uncommon to meet with people in whom bruising is very easily produced, although the coagulability of their blood is entirely normal.

But this assumption has been experimentally negated by Morawitz and Lossen. By connecting a cupping-glass with a mercurial manometer they were able to determine the average amount of negative pressure which was required to produce bruising in normal individuals, and it was found that just as great an amount of suction was necessary to lead to bruising in Case VII, who has been classified here as a severe case of haemophilia, and who bruised very easily with any direct trauma.

Besides, the existence of any other factor than deficient coagulability is not necessary to explain these haemorrhages after very slight injuries. The feeling that there must be some other cause is at root due to the very widely spread idea that haemophilia is a disease in which haemorrhage is produced more easily than in healthy people, whereas in reality it is not. The real distinction between a haemophilic and a normal person is not in the occurrence but in the *amount* of the bleeding. A normal person sustains a slight blow on the arm. A few capillaries are ruptured, but they are sealed almost at once by coagulation, and there are no signs of bruising. A similar degree of violence applied to a haemophilic will not lead at the moment to any greater haemorrhage; the difference arises later when haemorrhage continues for some time, so that such an amount of blood enters the tissues that signs of bruising appear.

Bleeding into a joint is often followed by a subacute inflammatory condition of the synovial membrane. Haemorrhage then arises with lesser degrees of trauma than are necessary when the membrane is healthy, and so it comes about that effusion may be produced into the joints of a haemophilic by

accidents, so trivial that they would not lead to any bleeding at all in a healthy joint. But the minimal degree of trauma necessary to cause haemorrhage into such a haemophilic joint will also lead to bleeding into the joint of a normal person in which there is an equal amount of synovial irritation. The end result will be different. In the haemophilic there will be a visible effusion, and in the normal person there will be no signs of haemorrhage. The distinction lies in the longer continuance of the haemorrhage in the one case than in the other, and not in its original inception.

The other theories of haemophilia, such as that it is due to disproportion between the quantity of blood and the size of the vessels, or that it is a manifestation of an organismal infection, &c., have been criticized by Sahli. They are for the most part purely speculative in character, and no practical evidence has been adduced in favour of any of them. For this reason, and in view of the positive evidence presented here, hereditary haemophilia is concluded to be directly due to a deficiency in the coagulability of the blood.

That is the opinion which all those who have worked at the subject in recent years already hold,⁹ and I have merely endeavoured to present a few further points in its support, for it is a matter of more than theoretical interest, since it raises the hope that researches into the cause of this defect in coagulation may yield knowledge on which an efficient treatment of the disease may be based. My thanks are due to the patients who, sometimes at the cost of some personal inconvenience, allowed these observations to be made.

Conclusions.

I. There is a deficient coagulability of the blood in each case examined.

II. The degree of the defect in coagulation corresponds with the degree of the severity of the clinical symptoms.

III. The coagulation of blood flowing from a wound is induced by thrombokinase added to it from the tissues, and the rapidity of coagulation varies directly with the amount of this thrombokinase. Much larger quantities of thrombokinase are required to produce rapid clotting in haemophilic than in normal blood. In a wound in a haemophilic, coagulation may therefore only occur in those parts where the concentration of thrombokinase is highest, i. e. on the sides of the wound. But this clot prevents the addition of further quantities of thrombokinase from the tissues, and when the amount of thrombin liberated from the primary clot is insufficient to lead to the complete coagulation of the blood in the centre of the wound, bleeding may continue indefinitely.

IV. Haemorrhage is no more easily induced in a haemophilic than in a normal person. The distinction is not in the occurrence but in the amount of bleeding.

⁹ Nolf and Herry must be excepted from this statement. In a paper published this year they revert to the idea of a special friability of the capillaries, believing that the delay in coagulation is not sufficient to explain the internal haemorrhages and the easily produced bruising in haemophiles.

The Cases investigated.

Case I. Male, aged 51. In his youth especially, he had suffered from all varieties of haemorrhage, for which he had been admitted to hospital no less than twenty-seven times, but for a number of years he had been entirely free from symptoms, so that shortly before I saw him he had ventured to have a tooth extracted. Serious haemorrhage followed and continued for ten days. He had two first cousins on his mother's side of the family who were haemophilics. One of them had died of haemorrhage.

Case II is a first cousin of Case V, and is a middle-aged man. He had had to be admitted to the hospital on seven occasions for continued haemorrhage, but for a long time he had not had haemorrhages. He considered himself to be quite cured.

Case III was nineteen years old. He was the brother of Case IV, and the first cousin of Case V. So far as he knew the disease first became apparent when he was eighteen months old. This is a history which appears to be often given, and on this ground it has been supposed by some that the condition only develops some time after birth. But this freedom from symptoms during the first year is probably due to the care with which babies are handled. Dr. Nacke of Kirchheim told me that he could usually say at birth which members of the Mampel family were going to be haemophilics from the bleeding from the cord, which continued in them even after it had been firmly ligatured. Several cases had died of such haemorrhages. This particular case was seldom free from an effusion into one or other of his joints. He had had several severe and dangerous haemorrhages, notably one from a cut on the scalp which bled for a fortnight.

For *Cases IV and V* I am indebted to Dr. Groves of Bristol, who has already published an account of their personal and family history in a paper on some of the surgical aspects of haemophilia. They were both cases with well-marked symptoms.

Cases VI, VII, VIII, and IX were members of the famous haemophilic family of Mampel, most of whose descendants still live in the village of Kirchheim near Heidelberg. The story of this family has been written several times in the last fifty years. The most recent account is by Lossen, who gives a family tree which goes back for many generations.

Case VI was a middle-aged man in whom the improvement which sometimes comes when youth is past was scarcely perceptible, although on the whole he considered himself to be rather better than when he was young. He was seldom, however, free from bruises, effusions into the joints, or bleeding from the gums. While he was under observation he suffered from an effusion into one of his elbow-joints and from several bruises following on trifling injuries.

Case VII was the boy on an examination of whose blood Morawitz and Lossen based their paper on the causation of the deficient coagulability in haemophilia. They give a full clinical history.

Case VIII was eleven years old and had a very similar history to his cousin, Case VII. Both were cases in which the symptoms were prominent.

Case IX was sixteen years old. At the time I saw him he was suffering mainly from recurrent attacks of haematuria. He had a deformity of the forearm similar to that described by Dr. Groves in Cases IV and V.

Cases X and XI were under the care of Dr. T. Y. Finlay, to whom I am indebted for the opportunity of observing them.

Case X was a severe case.

Case XI, who was from a different haemophilic stock, was the case described as being of only moderate severity.

I have to thank Mr. J. M. Cotterill for giving me facilities to investigate the coagulability of the blood in Case XII. The clinical history and an account of other investigations in this case will appear later. He was a middle-aged man in whom the evidence of a haemorrhagic tendency was very pronounced.

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